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Editorial

Sunset, or dawn of a new age for ovarian cancer vaccine therapy?

In this issue of *Gynecologic Oncology*, O'Cearbhaill et al. report the results of GOG255, a randomized double-blinded phase II trial aimed at determining if the polyvalent vaccine targeting ovarian surface antigens and administered with the adjuvant OPT-821 can prolong progression-free survival (PFS) or overall survival (OS) beyond that observed with OPT-821 alone. To be eligible subjects had to have epithelial ovarian cancer in a second or third complete clinical remission. In other words, this trial asks the question, "Is targeted immunization superior to non-specific immune stimulation by an adjuvant?" The short answer, unfortunately, is "no." The hazard ratio for PFS in the vaccine + OPT-821 compared to OPT-821 alone was 0.98 (95% CI: 0.71–1.36) and the median OS was 47 and 46 months respectively [1].

The investigational vaccine therapy was well tolerated with the most common adverse events related to injection site reactions, and very few grade 3/4 events of any kind (6.4% overall). The authors also investigated immunogenicity by evaluating pre- and post-vaccination IgM and IgG responses to each of the vaccine antigen. Immunoglobulin titer change occurred in a variable percentage of subjects across the different vaccine antigens, ranging from 7 to 49% and with the most frequent changes observed for the MUC1 antigen. However, a similar evaluation of antigen related immunoglobulin titers was not performed for the OPT-821 alone control arm. Since the vaccine targeted commonly expressed ovarian cancer cell surface antigens, it would be expected that subjects who received OPT-821 alone may have also had the potential to develop an immune responses to those vaccine antigens present on their tumors. It is therefore difficult to definitively conclude that the vaccine (rather than non-specific immune activation by OPT-821 adjuvant) was responsible for the observed IgM and IgG titer change results. Last but not least, extreme caution must be exercised in any consideration of the overall longevity of the study population. The overall survival in this study's population is significantly confounded by the selection bias resulting from the eligibility requirements for this trial (subjects had to be in a second or third complete clinical remission after recurrence, constituting a favorable prognostic group).

Interest in immunotherapy for ovarian cancer has been long-standing and continuously evolving. It is therefore useful to consider the results of this trial in this broader context. While it's tempting to draw comparisons between the results of this trial and more recent immunotherapy trials in ovarian cancer, it is important to note that enrollment on this trial occurred from 2010 to 2013. Readers may recall that first study reporting improved efficacy of ipiliumamb plus glycoprotein 100 (gp100) peptide vaccine compared to vaccine alone in patients with metastatic melanoma was published in 2010 [2]. Hence, this clinical trial was conceived and conducted in the pre-immune checkpoint inhibitor era. The efficacy of cancer vaccines in this time period was summarized in an editorial published by Dr. Steve Rosenberg in 2012 [3]. Citing two large reviews of multiple cancer vaccine clinical trials prior to 2010 [4,5], he noted "both [reviews] revealed an overall objective response rate of 3–4%, with only rare complete responders." Rosenberg goes on to conclude that "although no cancer vaccines capable of reproducibly mediating cancer regression have been described to date, this approach continues to receive considerable attention as a potential treatment for metastatic cancer, perhaps in part because of the allure of easy distribution by pharmaceutical companies and outpatient administration."

The place of vaccines in the current "post immune checkpoint era," landscape of cancer immunotherapy remains to be determined, and is the subject of intense investigation. However, it is important to recognize that the term "vaccine" encompasses many heterogeneous immunologic interventions aimed at enhancing the recognition and killing of cancer cells by the patient's immune system. Distinct from the antigen-immunogen approach use in the study by O'Cearbhaill et al., examples of other vaccine approaches include the use of modified dendritic cells [6] (a major class of antigen presenting cells), non-dividing cancer cells modified to secrete inflammatory cytokines [7], and DNA encoding tumor associated antigens [8]. Another differentiating aspect of vaccination strategies is whether the targets represent shared cancer antigens or private mutated proteins limited to a subset or even a single patient. The latter "personalized vaccine approach" involves whole exome sequencing to identify somatic mutations and the use of the corresponding mutated peptides to induce immune responses against neo-antigens. The proof of principle for this approach has been demonstrated in patients with melanoma [9,10].

Combining vaccine approaches with immune checkpoint blockade can serve to stimulate immunity and to mitigate immune-inhibitory pathways. This is an attractive approach supported by animal models and currently under investigation in over 30 clinical trials [11]. Despite the strong rationale, the combination of immune checkpoint blockade and vaccines may not be sufficient to result in increased clinical efficacy. For example, a key insight regarding the critical role of vaccine adjuvants was borne out of a recent study. Using a mouse model of melanoma, investigators found that the incomplete Freund's adjuvant, a constituent of many cancer vaccines, had a detrimental effect on PD1 and CTLA4 blockade-induced cancer-specific T cells [11]. This negative effect resulted from sequestration of effector T cells at the vaccination site leading to the recruitment of inflammatory monocytes and additional T cells, accompanied by their exhaustion and activation induced cell death. In contrast, viral vectors, or water-soluble peptide vaccine formulations based on dendritic cells, potently

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synergized with checkpoint blockade, and led to complete tumor regression, even in tumors that demonstrated resistance to CTLA4 and PD1 checkpoint blockade [11].

A number of promising innovations with potential to improve classical vaccine strategies are under active clinical investigation, and their discussion is beyond the scope of this editorial. However, examples of such approaches include: intratumoral administration of Toll-like receptor (TLR) and stimulator of interferon gene (STING) agonists, use of oncolytic viruses, and other in situ immune activation strategies that target pattern recognition receptors [12–15]. Last but not least, repurposing of attenuated virus vaccines for intratumoral application was recently reported, and has the advantage of rapid clinical translation and potential regulatory approval [16]. The overall aim of these strategies is to stimulate antitumor immunity and convert "cold" tumors into immune-infiltrated "hot" tumors. Successes and failures from this next wave of cancer vaccines will provide a better mechanistic understanding and rationale for combination immunotherapy strategies, and will hopefully translate into improvements in currently achievable clinical responses.

In summary, we are witnessing a time of transition from the old concepts of cancer vaccine therapy to a new era of multi-pronged immunotherapy and tumor microenvironment modulation. This will hopefully prove be a new dawn for cancer vaccine therapy in general, and especially, for ovarian cancer immunotherapy.

Author contributions

EH and AJ were involved in conception and preparation of this editorial.

Declaration of competing interest

The authors have no competing interests to disclose related to the study and results reported.

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